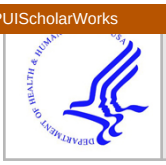

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Global White Matter Microstructural Abnormalities Associated with Addiction Liability Score in Drug Naïve Youth

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Abstract

Abnormalities in brain white matter (WM) structure have been reported in youths having a family history of substance use disorders (SUDs). It was hypothesized that these abnormalities constitute features of the liability for SUDs transmitted across generations. The association between severity of intergenerational risk for SUD, measured by the Transmissible Liability Index (TLI), and white matter microstructure was examined. Diffusion tensor imaging (DTI) measured WM microstructure in forty-four drug-naïve 10–14 year-olds (N= 19 with parental SUD). Metrics of WM microstructure (i.e., fractional anisotropy, radial diffusivity, mean diffusivity and axial diffusivity) were quantified across the whole brain and in four tracts of interest: anterior corona radiata, superior and inferior longitudinal fasciculi and superior fronto-occipital fasciculi. The TLI was completed by the youths, their parents and, when available, their teachers. The relationship between WM structure and TLI score across the entire group was evaluated using linear multiple regression and between group comparisons were also examined. Fractional anisotropy and radial diffusivity in multiple tracts across the brain were significantly associated with TLI scores. Confirming and extending prior research, the findings indicate that global atypicality in WM tracts was linearly related to liability for eventual SUD development in drug naïve youths.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all parents/guardians of child participants included in the study. Assent was obtained from all child participants.

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Keywords

diffusion; substance use disorders; adolescence; white matter

Introduction

The association between drug and alcohol use and white matter (WM) microstructural abnormalities throughout the brain is well established (Baker et al., 2013; Lin et al., 2013; Yeh et al., 2009). Evidence from animal models and human studies also suggests some such abnormalities may precede the onset of substance use and may even be related to risk for developing substance use disorders (SUDs). Animal models that involve perinatal neurodevelopmental alterations to prefrontal-temporal limbic network connectivity produce poly-drug SUD vulnerability that precedes actual experience with drug self-administration (Berg et al., 2014; Chambers et al., 2010).

WM microstructure in humans is primarily characterized using four metrics derived from diffusion tensor image brain scanning (Alexander et al., 2007): 1) *fractional anisotropy* (FA) indicates how directional the diffusion is and reflects the coherence of the underlying tissue or fiber organization, 2) *axial diffusivity* (AD) provides a measure of axonal integrity, 3) *mean diffusivity* (MD) measures the average amount of diffusion and describe the relative degree of anisotropy in a voxel (ranging from a perfect sphere to a pencil-like shape) and 4) *radial diffusivity* (RD) relates to myelin integrity. FA is driven by two forces – AD (along the principal eigenvector) and RD (along second and third eigenvector that are perpendicular to the direction of the fiber). Therefore, differences in FA can be caused by changes in AD, RD, or both. This makes FA sensitive to white matter microstructural pathology, but not very specific to the type of changes (e.g., radial or axial).

Specific to SUD risk in drug-naïve humans, *lower* FA has been observed in frontocortical, frontostriatal and parietocortical tracts (including the anterior, superior and posterior corona radiata (ACR; SCR; PCR) and superior fronto-occipital fasciculus (SFOF)) in 11–15 year-old youths who have parents with SUDs (Acheson et al., 2014). Lower FA has also been found in the ACR, superior and inferior longitudinal fasciculus (SLF/ILF), external capsule, anterior limb of the internal capsule and the optic radiation in youths having a family history of alcohol use disorders (Herting et al., 2011; Herting et al., 2010). In that sample, FA also mediated a relationship with alcohol family history and reaction time on a delay-discounting task. Another study (Wetherill et al., 2012) did not find differences between adolescents with and without family history of alcoholism on WM measures of frontoparietal tracts. Lastly, a study of young adults, many having substantial histories of drug and alcohol use, reported an interaction between alcohol exposure and familial risk that predicted reduction in WM integrity in the ILF and SLF, along with the forceps major tract (Hill et al., 2013).

In contrast to the above findings of *lower* FA among high risk youth, a smaller number also report *greater* FA in youth at high risk for SUD development. Adolescents with a family history of SUD had higher FA than comparison participants in 19 clusters spanning projection, association and interhemispheric white matter tracts (Squeglia et al., 2014). In a separate sample FA was positively correlated with self-reported risk taking (Berns et al.,

2009). In aggregate, the emerging findings, albeit not consistent across studies, suggest that white matter abnormalities presage substance use onset and are related to family history of SUD.

An important question that remains to be addressed concerns whether the WM abnormalities observed in youth at high risk for SUD have a genetic etiology. Numerous studies have reported that SUDs are heritable and elevated rates of the disorder(s) are seen in first-degree relatives. However, it is not yet practical to access individualized genetic testing to determine if a particular individual has a genetic predisposition for SUD. Furthermore, family history alone is a limited indicator of risk status because the majority of youths whose parents have a drug use disorder do not develop this disorder, and most youths who develop SUD do not have an affected parent (Vanyukov et al., 2003b). Consequently, comparing children of SUD + and SUD− parents can misclassify many individuals. To assess a complementary approach, this study utilized an individual measure of intergenerational risk for SUD that has been found to be superior to parental SUD in predicting offspring SUD development (Ridenour et al., 2011). Specifically, this project explored the relationships between WM microstructure and childhood vulnerability to SUD using the Transmissible Liability Index (TLI), an instrument validated to quantify intergenerational risk for SUD (Vanyukov et al., 2009). With most of the TLI's variance attributable to genetic factors (Vanyukov et al., 2009), it is the genetic component of risk measured by the TLI that has been shown to predict development of SUD (Vanyukov et al., 2014). WM microstructural abnormalities across the brain and in four tracts known to be atypical in high-risk youths, (Acheson et al., 2014; Berns et al., 2009; Herting et al., 2011; Hill et al., 2013; Squeglia et al., 2014) namely the ACR, SLF, ILF and SFOF were hypothesized in this study to be linearly associated with the severity of transmissible risk for developing SUD. To avoid type 2 error related to multiple comparisons, the analyses were confined to four tracts. In sum, the primary intent of this pilot analysis is to determine whether metrics of brain diffusion correlate with the magnitude of transmissible (parent to child) liability for developing SUD.

Material and Methods

Participants

English-speaking 10–14 year old male (N=29) and female (N=15) right-handed youth with a diverse range of addiction liability were recruited for study, as previously described (Hulvershorn et al., 2013; Hulvershorn et al., 2015). The sample consisted either of: (1) participants having biological fathers and at least one more first- or second-degree family member with lifetime SUD (other than/in addition to nicotine or alcohol use disorders; N=19) or (2) youths without a family history of psychiatric or SUDs (including nicotine; N=25; Table 2), recruited from the community. Paternal SUDs are summarized in Table 3. Mothers with SUD were not required for inclusion, in order to limit the amount of in utero drug exposure in the sample. Mothers, with or without SUD were interviewed about drug use during pregnancy. Youth were excluded if any use, including nicotine, during pregnancy was reported. The SUD offspring were identified with the assistance of addiction treatment providers along with community advertisements, and communication with schools and other healthcare providers.

To conform to an established addiction-risk model (Tarter et al., 2003), these youth participants with histories of parental SUD were also required to qualify for DSM-IV-TR criteria for attention deficit/hyperactivity-disorder (ADHD; any subtype), in addition to diagnosis of disruptive behavior disorders (i.e., conduct disorder (CD) oppositional defiant disorder (ODD), or disruptive behavior disorder (DBD NOS)). Youth who did not have a SUD family history also did not have current or history of psychiatric disorders or SUDs, with the exception of specific phobias, enuresis, encopresis, and learning disorders. This heterogeneous grouping of typically developing youth and youth with psychiatric disorders and family history of SUD were needed to allow for sufficient variability in TLI scores in the regression analysis.

Exclusionary criteria for all participants were (1) lifetime bipolar disorder, psychotic symptoms, pervasive developmental disorder, or SUD in the child; (2) current major depressive disorder; (3) current psychopharmacologic treatment other than psychostimulants (withheld on the days the assessment and scanning were conducted); (4) history of neurological disturbance; (5) Full Scale IQ below 80; (6) active or debilitating medical disorders; (7) substance use disorder during pregnancy; and, (8) Consumption of abusable drugs, including nicotine and alcohol, more than five times in their lifetime. Exclusionary criteria specific to the MR protocol were claustrophobia, pregnancy, left handedness and standard MRI contraindications (i.e., metal braces, metal prosthetics or implants, transdermal medication patches, metallic ink tattoos on the neck or face). To address heterogeneity in current or prior psychotropic medication exposure, analyses presented here ultimately excluded the four participants who were psychotropic medication naïve. In effect, this study constitutes a medically treated sample (n=15; and controls, n=25), with the high risk group reflecting the more severe segment of the affected population.

Transmissible Liability Index

The TLI was developed from data acquired during a longitudinal study of male youth initially assessed at age 11 before SUDs had developed. Youth with and without parental SUD were recruited and were compared on common risk factors for SUD and then eventually substance use, as they passed into the age of typical onset for the disorder (Vanyukov et al., 2003a; Vanyukov et al., 2003b). Briefly, the TLI was developed in several stages. First, constructs were derived from parent, child and teacher assessments and validated using exploratory and confirmatory factor analysis to characterize processes that have been frequently implicated to be related to SUD risk (e.g., aggression, hyperactivity, impulsivity, norm-violating behavior, sleep patterns, and cognitive flexibility). Next, the constructs that discriminated sons of SUD+/SUD− fathers were retained and the items comprising the constructs were submitted to second order exploratory factor analysis followed by confirmatory factor analysis. Lastly, item response theory (IRT) analysis was conducted on the final set of items which comprised the continuous latent trait of TLI to determine the threshold and discrimination parameter of each item and to estimate TLI score. According to the measurement model applied (Vanyukov et al., 2003a), regardless of what original scale or construct an item originates from (e.g., diagnostic evaluation tool, behavioral rating scale), the TLI derivation procedure ensured that this item is calibrated and

applied as an indicator of the *transmissible* component of SUD liability. A separate index was also developed for non-transmissible liability, but it was not used in this study.

The TLI has good predictive, discriminative and concurrent validity, with internal reliability of .93 at ages 10–12 and .95 at age 16. (Kirisci et al., 2009; Tarter et al., 2003; Vanyukov et al., 2009). Findings indicate that TLI has confirmed high heritability and predictive validity in SUD and drug use disorder cases (Kirisci et al., 2015; Vanyukov et al., 2015; Vanyukov et al., 2009). TLI has specifically predicted the development of cannabis and alcohol use disorders (Kirisci et al., 2009; Kirisci et al., 2013; Tarter et al., 2003). The measure quantifies risk on a continuous interval scale ranging from −4 (lower risk) to +4 (higher risk) (Vanyukov et al., 2003a). The Social Deviancy and Self-regulation subscales of the TLI were also calculated from the TLI yielding scores ranging from −4 to +4. In summary, the TLI is a recently developed continuous measure of intergenerational risk for drug use disorders consequent to consumption of illicit drugs.

Procedures

Children—Following informed consent/assessment using forms approved by Indiana University IRB, the participants received urine screens for recent use of cannabis, cocaine, ecstasy, methamphetamine, and opioids (Uritox Medical). None of the participants tested positive. Next, section i1A of the revised Drug Use Screening Inventory (Kirisci et al., 1995) was administered in a private setting to each participant to document lifetime substance use. The TLI (Vanyukov et al., 2009; Vanyukov et al., 2003b) was administered to the child and their parent as well as teachers, when available. The Kiddie-SADS Past and Lifetime (Kaufman et al., 1997) semi-structured psychiatric assessment was administered by a pediatric psychologist or psychiatrist to determine the presence or history of psychiatric disorders. Parents also completed a checklist to estimate stage of pubertal development.

Parents—After consent, the SUDs section of the Structured Clinical Interview for DSM-IV (SCID)-I/Non-Patient Edition (First et al., 2002) was used to ascertain the presence of SUD in the fathers. If the child's biological father was not available for an in-person or phone interview, the mother completed an informant version of the SCID interview. All mothers of children included in the sample denied drug or alcohol use during pregnancy.

Participant families were compensated for attending an initial 4–5 hour assessment session (parents plus child interview) followed by the MRI scan, completed within 2 weeks of the initial assessment session.

Imaging was performed in a Siemens 3T TIM Trio MRI scanner using a 32-channel receiver-only head coil. Each participant underwent diffusion tensor imaging (DTI), using a single-shot echo-planar imaging (SS EPI) sequence (7 minutes, 58 seconds). A double refocused spin echo was used to reduce eddy current effects. Sixty-eight transverse slices were acquired with 2mm slice thickness. Images were acquired along 48 non-collinear diffusion-weighted (DW) directions with gradients b = 1000 s/mm^2, TR/TE = 77/8300ms, Matrix: 128×128, FOV: 256×256m. Eight additional image volumes were acquired for each subject with b = 0 s/mm^2.

Data Analysis

To decrease the impact of motion artifacts and for quality control of the image data, we visually reviewed the diffusion-weighted image data slice by slice for all diffusion-weighted directions. Images with axial banding, blurring, rotation and dislocation were recorded. Five participants were excluded because of excessive motion artifacts in 8 diffusion-weighted image volumes (out of 48 original volumes), resulting in 44 participants reported here. Of the remaining participants, 27 of 44 had at least one but less than 4 diffusion-weighted image volumes removed from analysis. Overall, the deleted diffusion-weighted image volumes per subject were less than 5% of the original image volumes. The b matrix and diffusion-weighted direction table were also changed accordingly if there were deleted image volumes.

After initial image quality control for excessive motion artifacts, the diffusion-weighted data were fed into the data-preprocessing pipeline used by the FSL data analysis suite (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Each volume was motion and eddy current corrected before data processing. Motion correction was conducted by aligning the diffusion-weighted images to the b-value = 0 s/mm^2 image (Jenkinson et al., 2002). Corrected images with corresponding diffusion directions and b-values were reconstructed to form DTI images for each participant. A brain mask was obtained for each subject's DTI data by applying brain extraction tool (BET) of the FSL toolbox on the b-value = 0 s/mm^2 image volume. Individual DTI measures were FA, AD and RD.

The DTI data analysis used Tract-Based Spatial Statistics (TBSS) (Smith et al., 2004). First, nonlinear registration aligned all FA images to a 1×1×1mm standard-space template (FMRIB58_FA). Next, the FA image was aligned to the image of all other participants and to the most representative FA image (i.e., the smallest amount of average warping that was needed to align to the target). This latter image was then affine-aligned into MNI152 standard space, and every image was transformed into 1×1×1mm MNI152 space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. This procedure yielded a standard-space version of each subject's FA image. A skeletonized FA map was then created from the sample mean FA map, with a threshold set at 0.2, to ensure that only WM tracts were included. RD, MD and AD maps were identically transformed to this FA skeleton.

Next, linear regression (controlling for age, sex, full scale IQ and socioeconomic status) was performed at the group level to determine whether there was a relationship across all participants between TLI total score (final score represents combination of parent, child and teacher score, when available) and FA, RD, MD and AD across the entire brain. The same procedure was used to assess the relationship between the TLI subscale scores (Social Deviancy and Regulation) and the four WM measures. A threshold-free cluster enhancement (TFCE) technique was used to correct for multiple comparisons at p-value less than 0.05 (46). Next, an *a priori* region of interest approach was utilized to examine four WM tracts previously implicated in high-risk samples: ACR, SLF, ILF and SFOF. To examine WM in these regions, bilateral anatomical regions of interest were formed using the conjunction of the ICBM-DTI-81 parcellation atlas with the derived FA skeleton. Mean FA, RD, MD and AD were then extracted from each region. Linear regression analyses, controlling for age,

sex, full scale IQ and socioeconomic status were performed (separately for each region and for the whole brain analysis) to determine whether each region's FA, RD, MD and AD were related to TLI total and subscale scores. To estimate an effect size, we calculated the standardized regression coefficient (β) for TLI scores with DTI measures. Mean FA and RD were extracted for each subject within these clusters, and the standardized regression coefficients were calculated, controlling for age, sex, IQ, and socioeconomic status. Sex by TLI interactions were also examined.

As a secondary analysis, high and low risk groups were compared across the whole brain and within each of the four regions of interest, again controlling for age, sex, IQ and socioeconomic status.

Results

The TLI total (M = 0.81, S.D. = 0.91), Self-regulation subscale (M = 0.64, S.D. = 0.86) and Social Deviance subscale (M = 0.87, S.D. = 0.69) indicate that the overall sample skewed toward elevated SUD risk. This is expected considering that approximately half of the sample had fathers with SUDs plus childhood externalizing disorders. The entire sample had complete TLI responses from the parents and children, while only 29% had additional responses provided by teachers.

Imaging Results

Regression Analyses

Across the sample, the TLI total scores were linearly related to two of the four WM measures (i.e., FA, RD, MD or AD) in the whole brain analysis. Specifically, FA (Table 4 & Figure 1) and RD (Table 5 & Figure 2) were both associated with TLI total score in a large number of WM tracts spread across the brain. The direction of the TLI and DTI relationships are shown in Figure 3 (i.e., FA positively related to TLI and RD negatively related to TLI). Sex by TLI interactions were not found. TLI subscales were not significantly associated with any of the WM measures.

Associations were also not observed between TLI total or subscales, nor any of the diffusion measures within the four *a priori* selected regions of interest, although trend-level findings were found in the left ILF (p=0.060) and right ACR (p=0.065) ROIs. Of note, 2 of the 4 ROIs (SLF, SFOF) were not significantly associated with TLI in any voxel in the brain, while the other 2 ROIs did overlap with the whole brain findings (Table 6), substantially in the left ILF and right ACR. Hence, the majority of the findings from the whole brain analysis were in regions distinct from the ROIs.

Between Group Comparison

No between group differences emerged during either the whole brain or region of interest comparison, when controlling for age, sex, IQ and socioeconomic status.

Discussion

This study examined the relationship between white matter (WM) microstructure and childhood transmissible liability for SUD (Tarter et al., 2003; Vanyukov et al., 2009). To briefly recapitulate the findings, WM microstructural measures were positively associated with TLI scores in 10–14-year-olds in numerous regions spanning all quadrants of the brain. Given the corresponding negative association of TLI with RD (and absence of an association with AD in any tracts), we speculate that our findings of increased FA were driven by decreased RD (i.e., perpendicular, rather than axial diffusivity). The findings of an association between *increased* FA and magnitude of transmissible risk is opposite to results obtained in adults (Gruber et al., 2011; Li et al., 2013; Yeh et al., 2009), adolescents having alcohol use disorder as well as other types of SUDs (Jacobus et al., 2009; Jacobus et al., 2013a; McQueeny et al., 2009) and youths having a positive SUD family history (Acheson et al., 2014; Herting et al., 2010). The findings are, however, consistent with results reported in a sample of alcohol-abusing adolescents with juvenile-justice involvement (Thayer et al., 2013). The reasons for the disparate findings remain unclear, although it is noteworthy that conduct problems, which are highly represented in our sample, have also been associated with *increased* FA in two other studies focusing on youth (Passamonti et al., 2012; Thayer et al., 2013). Other studies in high risk samples also found adolescents with greater WM coherence were more prone to engage in earlier and riskier behavior (Berns et al., 2009; Squeglia et al., 2014). This increase in maturation of WM may be an advantage because it could promote early autonomy. However, early maturation may also create vulnerability via increases in precocious sensation seeking behaviors.

Tracts identified as having a relationship with TLI score carry neural impulses between the brainstem and the cerebral cortex (Jellison et al., 2004), as well as between cortical hemispheres (i.e., corpus callosum). Thus, while not conclusive, the present results indicate that specific WM microstructural abnormalities in multiple tracts throughout the brain may predate drug abuse and are related to transmissible risk for SUD. Regressing a trait (i.e., transmissible liability for addiction) across a heterogeneous sample as we have done here, has revealed microstructural abnormalities in multiple relevant regions, most of which have been previously implicated in prior ROI-based DTI studies of high risk vs lower risk populations (typically a small number of regions in each paper). Using this method, rather than strictly an ROI approach which can only examine a small number of regions in a given sample due to multiple comparisons limitations, we demonstrate preliminary evidence for broad disruptions throughout the brain, validating findings from multiple studies reviewed above (e.g., anterior and posterior CR, internal capsule, ILF) and implicating novel regions which have not been consistently reported, such as the thalamic radiation, forceps major and minor.

Given the vast influence of these tracts across multiple brain regions, a variety of cognitive, emotional and behavioral impairments could, in theory, result from these microstructural deficits. In fact, WM microstructural abnormalities in adolescents have been shown to co-vary with cognitive and behavior disturbances. Low FA among cannabis- and alcohol-using adolescents in the temporal lobe was associated with attenuation of attention, working memory and information processing speed (Bava et al., 2010). Low FA in occipital tracts

was associated with working memory and complex visuomotor sequencing deficits in adolescent substance abusers, whereas low FA in anterior regions was associated with low verbal memory performance (Bava et al., 2010). Lower FA in the SLF and posterior CR in juvenile justice-involved youth with problem alcohol use was related to increased impulsivity (Thayer et al., 2013). Notably, low fronto-limbic WM FA in adolescent alcohol and marijuana users has also been found to forecast delinquent behavior up to a year and a half later (Jacobus et al., 2013b).

In contrast to prior studies employing family history as the marker of risk status (Acheson et al., 2014; Herting et al., 2010), significant differences between high and low risk participants in this sample were not observed. Of note, our sample was both smaller in number of participants and younger in age than those in prior addiction risk WM studies. During adolescence, white matter volume increases in all areas of the brain, along with microstructural indicators of tract organization, such as FA (Giorgio et al., 2008). The ACR has been shown to have continued maturity (i.e., increasing FA) throughout childhood and into adolescence (Asato et al., 2010), while the SLF (Giorgio et al., 2008; Peters et al., 2012) has been shown to mature into adolescence. Thus differences reflecting atypical development may not yet be entirely evident in our sample. The findings underscore the need for prospective investigation to delineate, in tandem, the association between microstructural abnormalities and severity of the psychological manifestations comprising transmissible risk for SUD.

Several limitations of this pilot study are noteworthy. Youths with high TLI scores were all offspring of individuals with SUD, thus we are unable to separate the effects of parental history of SUD and the presence of childhood externalizing traits. This design aimed only to recruit youth with a wide range of transmissible SUD liability. Future studies examining youths with elevated TLI scores, with and without parental SUD, are needed to address this limitation. Second, the mean TLI score in the sample was higher than the general population, as was the mean score for the youth without parental SUD. Third, given that all but four of the high risk participants were exposed to psychotropic medications at some point in their lives, we opted to exclude those participants from imaging analyses. The possibility that these medications impacted WM microstructure cannot be discounted. The findings from these youth with clinically significant psychopathology are limited by psychotropic medication exposure. Relatedly, clinical indications of withdrawal from stimulant medication were not observed. However, this does not preclude the possibility that subtle withdrawal effects impacted the results. To our knowledge, a 24 hour washout period is sufficient for any withdrawal effects to resolve. Fourth, the TLI has only been validated in males, thus predictive validity of SUD development in female youth is unknown (Vanyukov et al., 2009). Furthermore, while previous studies have reported that alcohol and other drugs of abuse may have a greater impact on WM structure of female adolescents (Elofson et al., 2013; Thatcher et al., 2010), we were underpowered to adequately examine gender effects, although we report no sex by TLI interactions.

In sum, transmissible (i.e., intergenerational) liability score for SUD is positively associated with WM microstructural abnormalities in a heterogeneous group of 10–14-year-old youths. This method is promising and warrants replication in a larger sample. Regions supplied by

fibers from these tracts have been previously associated with SUD risk. Based on research showing strong genetic influence on WM tracts and findings herein demonstrating a correlation between transmissible risk and WM microstructure (Enoch, 2012; Vanyukov et al., 2003b), it is important to identify strategies that can mitigate the neurobiological abnormalities underlying the psychological disposition associated with SUD vulnerability.

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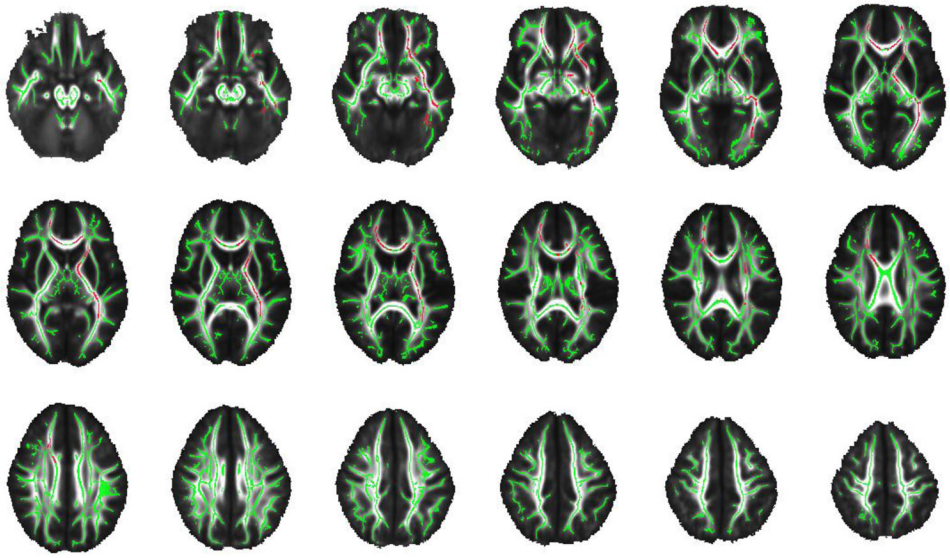

Figure 1.

White matter tract regions with a significant relationship between fractional anisotropy (FA) and transmission liability index, controlling for age, sex, IQ, and SES ($p < .05$, corrected for multiple comparisons). Brains are shown in radiological view (right = left).

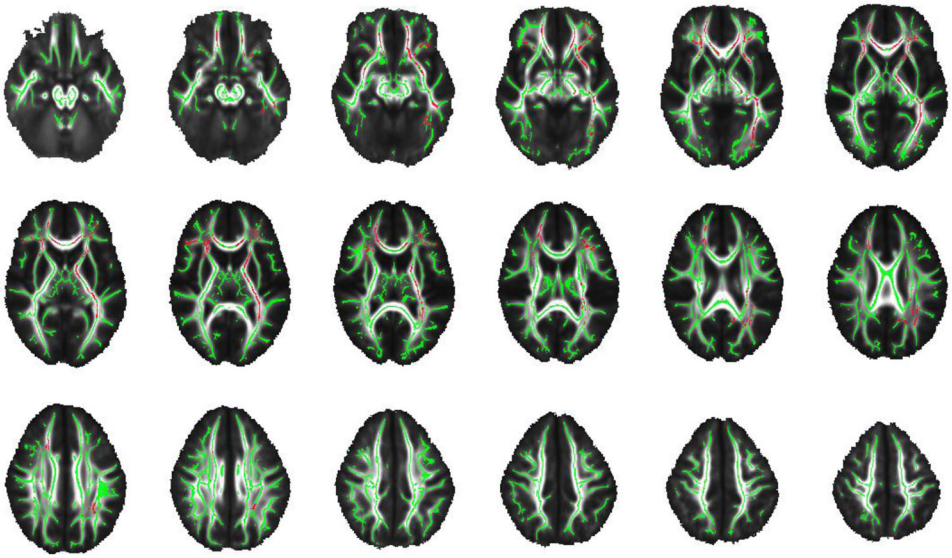

Figure 2.
White matter tract regions with a significant relationship between radial diffusivity (RD) and transmission liability index, controlling for age, sex, IQ, and SES ($p < .05$, corrected for multiple comparisons). Brains are shown in radiological view (right = left).

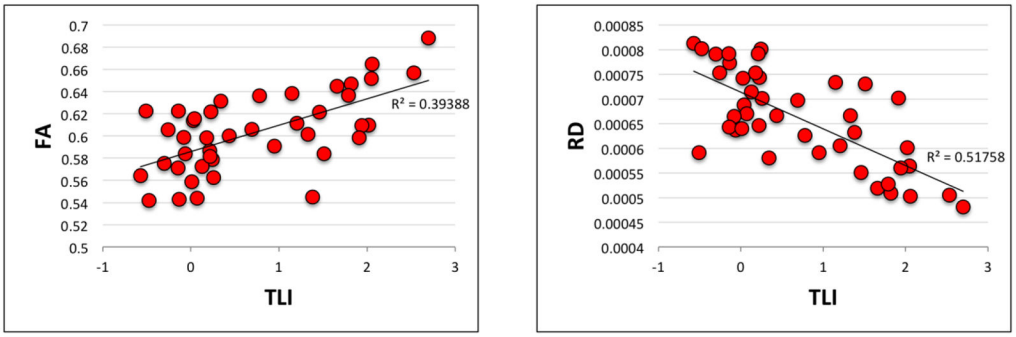

Figure 3.

Scatterplots depict the relationship between TLI and mean FA/RD within the single largest significant cluster for each measure.

Table 1

White matter tract and terminology abbreviations

Term	Abbreviation
Anterior Cingulate Cortex	ACC
Axonal Diffusivity	AD
Anterior Corona Radiata	ACR
Diffusion Tensor Imaging	DTI
Fractional Anisotropy	FA
Inferior Fronto-Occipital Fasciculus	IFOF
Inferior Longitudinal Fasciculus	ILF
Mean Diffusivity	MD
Posterior Corona Radiata	PCR
Radial Diffusivity	RD
Superior Corona Radiata	SCR
Superior Fronto-Occipital Fasciculus	SFOF
Superior Longitudinal Fasciculus	SLF
Transmissible Liability Index	TLI
White Matter	WM

Table 2

Characteristics of the sample (N = 44)

Females (%)	15 (34%)
Age	12.5 (1.26)
Race	
Caucasian	17 (39%)
African American	19 (43%)
Other	8 (18%)
WISC-III Full Scale IQ	105.0 (13.0)
SES (Family Income)	2.80 (1.56)
Tanner Stage of pubertal development	2.74 (1.20)
Paternal Substance Use Disorder	19 (43%)
Participants with any drug use	2 (4.5%)
Total # of lifetime drug use instances	4
Participants with externalizing disorders	19 (43%)
Participants with current anxiety disorder	6 (14%)
Past psychotropic medication use	19(43%)
Current psychotropic medication use	8(18%)

Table 3

Paternal DSM-IV substance use disorders present in the total sample (N=20 youth).

	# of Fathers Diagnosed
Alcohol Dependence	13
Alcohol Abuse	2
Cannabis Dependence	11
Cannabis Abuse	3
Cocaine Dependence	10
Hallucinogen Dependence	1
Opiate Dependence	6
Opiate Abuse	1
Sedative Dependence	1
Polysubstance Dependence	6

Number of SUD Diagnoses Per Individual	# of Individual Fathers
1 SUD diagnosis	4
2 SUD diagnoses	6
3 or greater diagnoses (includes polysub.)	10

Table 4

Association of TLI to fractional anisotropy.

Tract	MNI Peak	Size (mm^3)	Standardized Beta Coefficient
Corpus callosum (genu)	(−12, 33, 2)	2170	0.682
L Posterior thalamic radiation	(−34, −61, −1)	1755	0.610
L Internal capsule	(−14, −6, 7)	712	0.565
R Inferior fronto-occipital fasciculus	(20, 52, 6)	343	0.632
Corpus callosum (body)	(16, 16, 28)	203	0.405
R Forceps minor	(20, 48, 21)	143	0.590
R Anterior corona radiata	(20, 31, 28)	95	0.514
L Superior corona radiata	(−26, 1, 24)	77	0.246
L Anterior corona radiata	(−23, 25, 7)	65	0.455
R Anterior corona radiata	(24, 46, −2)	45	0.322
Corpus callosum (body)	(0, 16, 22)	43	0.502
L Anterior corona radiata	(−19, 53, 1)	34	0.202

Clusters with a significant positive relationship between TLI and fractional anisotropy, after controlling for IQ and SES (only clusters >30 mm^3 listed; $p < .05$, corrected).

Table 5

Association of TLI to radial diffusivity.

Tract	MNI Peak	Size (mm^3)	Standardized Beta Coefficient
L Inferior fronto-occipital fasciculus	(19, 29, 29)	2136	−0.651
L Posterior limb of internal capsule	(−28, −26, 10)	1960	−0.484
R Anterior corona radiata	(26, 31, 8)	1145	−0.557
L Anterior limb of internal capsule	(−28, 33, 20)	733	−0.451
L Posterior corona radiata	(−31, −53, 29)	375	−0.236
L Inferior fronto-occipital fasciculus	(−22, 22, −12)	218	−0.341
R Anterior corona radiata	(35, 36, −4)	195	−0.286
L Forceps major	(−22, −61, 23)	146	−0.472
R Anterior limb of internal capsule	(29, 18, 1)	94	−0.372
L Anterior corona radiata	(−26, 22, 2)	83	−0.546
L Anterior limb of internal capsule	(−20, 20, 2)	78	−0.468
L Anterior limb of internal capsule	(−20, 14, 11)	64	−0.418
R Inferior fronto-occipital fasciculus	(34, 2, −11)	52	−0.375
L Posterior corona radiata	(−29, −50, 25)	47	−0.320
L Anterior corona radiata	(−33, 50, 9)	38	−0.523
L Inferior longitudinal fasciculus	(−36, −58,−11)	36	−0.452
L Short-range frontal association fibers	(−32, 60, −6)	36	−0.490
L Inferior longitudinal fasciculus	(−28, −29, −5)	34	−0.339
L Tapetum	(−29, −39, 16)	33	−0.214
L Forceps major	(−27, −61, 20)	31	−0.488
L Anterior corona radiata	(−23, 34, 9)	30	−0.389

Clusters with a significant negative relationship between TLI and radial diffusivity (RD), after controlling for IQ and SES (only clusters >30 mm^3 listed; $p < .05$, corrected).

Table 6

Percentage of voxels in the regions of interest that are significantly related to TLI score ($p<0.01$ after multiple comparisons correction using TFCE).

Fractional Anisotropy	
R ACR: 8.4%	L ACR: 23.4%
R SLF: 0%	L SLF: 0%
R ILF: 0%	L ILF: 43.8%
R SFOF: 0%	L SFOF: 0%
Radial Diffusivity	
R ACR: 41.6%	L ACR: 20.8%
R SLF: 0%	L SLF: 0%
R ILF: 0%	L ILF: 25.3%
R SFOF: 0%	L SFOF: 0%

Abbreviations: R=right; L= left; ACR=anterior corona radiata; SLF=superior longitudinal fasciculus; ILF=inferior longitudinal fasciculus; SFOF=superior fronto-occipital fasciculus